Dermatologic and Ophthalmic Drugs Advisory Committee Meeting
September 9, 2003

Application# STN BL 125075/0 — Efalizumab
Genentech, Inc.

Proposed Indication: For the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis

Questions to the Committee for Discussion

Efficacy Outcomes

1)
Efalizumab was studied in four randomized, placebo-controlled phase 3 trials in patients with stable, chronic, moderate to severe plaque psoriasis. The primary efficacy assessment was the proportion of patients with ≥75% improvement from baseline in PASI (Psoriasis Area and Severity Index) score. The static physician's global assessment (sPGA), analyzed for the proportion of patients achieving the "minimal" or "clear" categories, was a secondary outcome.

At the end of a 12- week treatment period, the 1 mg/kg/wk efalizumab-associated difference between groups ranged between 17-37% on PASI 75 proportions and 16-29% on sPGA proportions:

Outcome Assessment	Study	Placebo	Efalizumab	Difference
	2058	n = 170	n = 162	
		2%	39%	37%
	2059	n = 122	n = 232	
PASI 75		5%	22%	17%
	2390	n = 187	n = 369	
		4%	27%	22%
	2600	n = 236	n = 450	
		3%	24%	21%
	2058	n = 170	n = 162	
		3%	32%	29%
	2059	n = 122	n = 232	
sPGA		3	19%	16%
	2390	n = 187	n = 369	
		3%	26%	23%
	2600	n = 236	n = 450	
		4%	20%	16%

Please discuss the strength of these data (e.g., effect size, robustness, consistency, etc.). Do these data provide sufficient evidence that efalizumab has efficacy in patients with moderate to severe chronic plaque psoriasis?

[Please note that the question of benefit-risk comparison will be specifically discussed later, after discussion of safety related questions.]

2)
In two of the phase 3 studies patients who achieved a PASI 75 response at the end of the 12-week treatment period were studied in paradigms of either efalizumab withdrawal until relapse or continued treatment.

One portion of Study 2058 examined efalizumab-treated patients who achieved a PASI 75 response and were observed off treatment until clinical relapse (defined as loss of at least 50% of the PASI score improvement that had occurred by week 12 of the first treatment course). They were then re-randomized to either placebo or efalizumab for a second 12-week treatment course. Although the numbers are small and there is a large amount of missing data, 17/55 (31%) of the patients re-randomized to efalizumab regained a PASI 75 response, compared to none of the 27 patients re-randomized to placebo.

In Study 2059, patients who achieved a PASI 75 response at week 12 were immediately re-randomized to receive efalizumab or placebo for a second contiguous 12-week treatment period (no off-treatment delay until relapse). The following results were observed following re-randomization:

	Placebo	Efalizumab
	n = 40	n = 79
Did not Relapse	13 (33%)	73 (92%)
Maintained PASI 75	8 (20%)	61 (77%)

a) The sponsor has proposed weekly efalizumab injections without any specific duration of treatment. Please discuss the strength of the efficacy data on intermittent vs. continuous use. If approved, do the data support a recommendation for continuous administration?

b) Are additional studies warranted to investigate an intermittent efalizumab treatment regimen? Note that if efalizumab is licensed, such studies can be conducted in the postmarketing period. If studies are warranted, please suggest optimal study designs.

Safety of Efalizumab

Specific safety issues include the following:

3) Psoriasis-related adverse events

Among over 2700 psoriasis patients treated with efalizumab (including during the placebo-controlled and extension studies), 19 (0.7%) experienced a serious adverse event of psoriasis. Some of these occurred during treatment with efalizumab, but most (14/19) followed discontinuation of efalizumab. A psoriasis-related adverse event of any severity (serious and non-serious) occurred in 52/1620 (3.2%) efalizumab-treated patients and 10/715 (1.4%) placebo patients.

a) Do these data suggest a signal with respect to rebound/disease-worsening in a proportion of patients?

b) If licensed, how should this information be conveyed in the physician's labeling?

c) Should the sponsor be asked to develop more comprehensive data regarding psoriasis rebound? If so, what specific studies or data collection would be potentially useful in managing this risk?

4) Arthritis and Other Inflammatory Adverse Events

Among all patients treated with efalizumab, 15 cases of serious adverse events of arthritis representing 0.6% of the studied population were observed. This includes one case in association with other findings of inflammation (fever, cellulitis and positive ANA). None of these cases occurred during the placebo-controlled portions of the clinical trials; all occurred during extension studies.

The proportion of patients with arthritis-related adverse events of any severity (including events of psoriatic arthritis, osteoarthritis and unspecified arthritis) during the placebo-controlled portions of the clinical trials were comparable between the placebo-treated patients (n=715, 2.2%) and patients treated with 1.0 mg/kg/wk efalizumab (n=1213, 2.4%). However, there was a suggestion of a higher proportion of patients with arthritis-related adverse events (3.9%) among those who received the 2.0 mg/kg/wk dose of efalizumab (N=407).

Rare cases of other inflammatory adverse events have also been noted in association with the use of efalizumab [e.g. transverse myelitis (1 case), interstitial pneumonitis (2 cases), idiopathic hepatitis (1 case)].

a) Do these data raise concerns regarding the risk of arthritis and other inflammatory adverse events?

b) Please discuss whether specific efforts on the part of the company are warranted to obtain additional information on the risk, management, and consequences of inflammatory adverse events. If so, what types of additional studies and/or databases would be most useful?

5) Thrombocytopenia

Thrombocytopenia that was consistent with an immunologically mediated mechanism occurred in a small number of efalizumab treated patients. Overall, eight patients experienced platelet counts of less than 50,000 cells/mm^3 (NCI-CTC Grade 3 adverse event)[1]; 5 were hospitalized and treated with steroids for their thrombocytopenia. Efalizumab was discontinued.

a) Do these data indicate an association between efalizumab and thrombocytopenia?

b) Should the company be asked to obtain additional data to more fully characterize this risk?

c) Please discuss whether the data are sufficient to allow recommendations on the management of this risk.

d) Is it appropriate to recommend that patients be monitored for thrombocytopenia if efalizumab is approved for marketing?

[1] One of the 8 had a platelet count of 52,000 but is included.

6) Safety of long-term continuous treatment

The current paradigms for the treatment of psoriasis requiring systemic treatment include continuous long-term treatment and intermittent and/or rotational therapy. The latter minimizes exposure to individual agents and may ameliorate drug toxicities that potentially are of a cumulative nature (e.g., hepatic toxicity with methotrexate and nephrotoxicity with cyclosporine).

In the efalizumab safety database, approximately 2400 patients received efalizumab weekly for 12 weeks of continuous treatment, 939 for 24 weeks of continuous treatment and 218 for one year of continuous treatment. These numbers are higher than the minimal ICH recommendations for safety database for products intended to be used chronically[2]. However, the agency may request that larger numbers of patients be exposed if warranted based on specific issues that require further evaluation.

a) Please discuss whether the submitted safety information on efalizumab use is sufficient to assess safety questions relating to long-term continuous treatment with efalizumab.

b) Please comment on any specific issues that may warrant further long-term risk assessment. Please include in your discussion the potential concerns regarding serious infections or malignancies. Please also include immunogenicity, which may potentially be a particular concern with intermittent treatment. .

c) Please comment on the potential need for long-term monitoring of immune function using clinical and laboratory assessments including the ability to respond to recall antigen and safety and efficacy of vaccines with efalizumab use.

[2] ICH recommendations for safety databases – overall experience of 1500 patients exposed at any dose, 300- 600 at the recommended dose for at least 6 months, 100 at the recommended dose for at least 12 months

Overall Risk-Benefit and Patient Population

6)
Based on the existing safety and efficacy information, please discuss which population of patients may be the most appropriate for use of this product.

The sponsor has proposed that the indicated population be "adult patients with moderate to severe plaque psoriasis." Eligibility criteria permitted enrollment of individuals who had received prior systemic therapy or phototherapy as well as those naïve to such prior therapies. The entry criteria excluded patients who did not have chronic (diagnosed for at least 6 months) plaque psoriasis at baseline. Patients who were not clinically stable for at least 3 months were also excluded.

a) Should the use of efalizumab be limited to patients who have failed or had an inadequate response to phototherapy or systemic therapy?

b) Should the use of efalizumab be limited to patients with moderate to severe plaque psoriasis who have stable, chronic disease?

7)
In light of the above discussion as to which patients may be the most appropriate for use of efalizumab, is the overall risk-benefit comparison for use of efalizumab favorable? *(Please vote on this question.)*

Studies in Pediatric Populations

8)
If it is determined that efalizumab is safe and effective for use in adults, please discuss the following issues.

a) Should efalizumab be studied in pediatric patients with psoriasis? If so, please discuss the optimal timing of such studies relative to accumulation of additional post-marketing safety data in adults.

b) What additional studies should be carried out in the pediatric population to fully assess safety and efficacy? Please include in your discussion the potential for loss of response to recall antigens and the potential for impact on response to childhood vaccines.

Study of Efalizumab with Concomitant Systemic Antipsoriasis Therapies

9)
In the clinical trials other systemic immunosuppressants and antipsoriasis medications were prohibited. If a patient developed a psoriasis-related adverse event requiring alternative systemic therapy, he/she was to immediately stop the study drug.

Please discuss whether efalizumab should be studied in combination with other systemic antipsoriasis medications, either long term or for a defined period of overlap?